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Nonsyndromic Hearing Impairment: Unparalleled Heterogeneity

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The Past

Prior to 1994, only three loci for nonsyndromic hearing impairment (NSHI) had been identified. In the late 1980s, a sex-linked form of NSHI was mapped to Xq13-q21.1 in Mauritian (Wallis et al. 1988) and Dutch (Brunner et al. 1988) kindreds in which affected individuals had prelingual severe to profound progressive mixed hearing impairment associated with diminished stapedial mobility and perilymphatic gushers at stapedectomy (Brunner et al. 1988). Four years later, an autosomal dominant locus was mapped to 5q31 in a large extended Costa Rican kindred that had emigrated from Jerez de la Frontera, Spain, during the early 1600s. Clinically, this type of NSHI was characterized by low-frequency hearing impairment beginning at ~10 years of age and ultimately progressing to profound, irreversible, bilateral impairment, over all frequencies, by age 30 years (Léon et al. 1992). The third locus, a mitochondrial mutation, was recognized in a large Arab-Israeli pedigree with maternally inherited NSHI. An A→G transition common both to this family and families with maternally inherited aminoglycoside-induced hearing impairment was identified in a highly conserved region of the 12S rRNA gene (nt 1555) (Prezant et al. 1993). Affected individuals had severe to profound NSHI across all frequencies, which was either congenital or rapidly progressive during early childhood (Jaber et al. 1992).

Prelingual NSHI

The incidence of prelingual hearing impairment is ~1/1,000 births, of which approximately one-half is thought to have a genetic origin (Fraser 1976; Morton 1991). In 30% of patients with prelingual deafness, additional anomalies are present (syndromic hearing impairment). Within the prelingual NSHI category, inheritance is most commonly autosomal recessive (75%–80%), followed by dominant (20%–25%) and X linked (1%–1.5%) (Stevenson and Cheeseman 1956; Chung et al. 1959; Fraser 1976; Hu et al. 1987; Cohen and Gorlin 1995).

Until the 1990s, most studies on hereditary deafness focused on prelingual deafness, since the patients were easily ascertained through schools and institutions for the deaf. It was generally believed that localizing genes for nonsyndromic prelingual deafness was a formidable undertaking, for several reasons: (i) prelingual NSHI is inherited, for the most part, in an autosomal recessive way; (ii) assortative matings are common within the deaf community; and (iii) epidemiological studies had indicated significant heterogeneity within the NSHI phenotype (Chung et al. 1959; Chung and Brown 1970; Morton 1991). Assortative matings introduce several deafness genes into a single pedigree, and genetic heterogeneity precludes pooling of families for linkage studies. In spite of these perceived obstacles, however, during the past 3 years >10 new gene localizations for recessive NSHI have been reported (table 1). These studies have been successful for two reasons. First, localization studies have been performed in large multigenerational inbred families from ethnically isolated regions. Because of their high degree of consanguinity, these multiplex families are large enough to generate significant LOD scores for linkage within a single pedigree. Furthermore, there is no assortative mating in these ethnically isolated regions. Second, it was not realized until the recent work by Fukushima et al. (1995*a*) that autosomal recessive deafness genes also can be mapped in small consanguineous multiplex families with ≥3 affected patients.

Postlingual NSHI

Systematic studies to determine the frequency and mode of inheritance in postlingual NSHI are not available. However, many families with hereditary postlingual NSHI have been described (Gorlin 1995; Online Inheritance in Man 1996), and the inheritance pattern is autosomal dominant in nearly all of them. Affected persons in these families develop normal speech and often retain partial hearing for decades. Consequently,

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Table 1

Gene Localizations for Autosomal Recessive NSHI

Locus	Location	Frequency	Onset	Type[a]	Reference
DFNB1	13q12	All	Prelingual	Stable	Guilford et al. (1994*a*)
DFNB2	11q13.5	All	Pre- and postlingual	Unspecified	Guilford et al. (1994*b*)
DFNB3	17p11.2-q12	All	Prelingual	Stable	Friedman et al. (1995)
DFNB4	7q31	All	Prelingual	Stable	Baldwin et al. (1995)
DFNB5	14q12	All	Prelingual	Stable	Fukushima et al. (1995*a*)
DFNB6	3p14-p21	All	Prelingual	Stable	Fukushima et al. (1995*b*)
DFNB7	9q13-q21	All	Prelingual	Stable	Jain et al. (1995)
DFNB8	21q22	All	Postlingual	Progressive	Veske et al. (1996)
DFNB9	2p22-p23	All	Prelingual	Stable	Chaib et al. (1996*a*)
DFNB10	21q22.3	All	Prelingual	Stable	Bonné-Tamir et al. (1996)
DFNB11	9q13-q21	All	Prelingual	Stable	Scott et al. (1996)
DFNB12	10q21-22	All	Prelingual	Stable	Chaib et al. (1996*b*)
DFNB13	Reserved[b]				
DFNB14	Reserved[b]				
DFNB15[c]	3q21.3-q25.2 and/or 19p13.3-p13.1	All	Prelingual	Stable	R. J. H. Smith, unpublished data

[a] All loci are responsible for sensorineural hearing loss.

[b] Localization has been reported to HUGO Nomenclature Committee but has not yet been published.

[c] A genomewide search demonstrated homozygosity by descent on chromosomes 3q and 19p in the family used to localize DFNB15. Both regions generated an identical LOD score of 2.78, the maximum obtainable LOD score in this family.

they seldom integrate into the deaf community and usually marry normal hearing persons. In the studies using these large families, >10 genes for dominant hearing impairment have been mapped during the past 3 years (table 2).

Autosomal Loci

To date, 13 autosomal recessive and 13 autosomal dominant NSHI gene localizations have been reported (tables 1 and 2). Dominant loci have the prefix "DFNA," and recessive loci the prefix "DFNB." In the recessive group of families, hearing impairment is prelingual and profound, with one exception: the family linked to DFNB8 has a postlingual, progressive impairment, although the onset of impairment is early and progress is rapid compared with those in families with dominant postlingual NSHI (Veske et al. 1996). In pedigrees with dominant NSHI, linked families have postlingual hearing impairment, with three exceptions: single families linked to either DFNA3 (Chaib et al. 1994), DFNA8 (Kirschhofer et al. 1996), or DFNA12 (G. Van Camp, unpublished data) show moderate to severe prelingual hearing impairment that is stable or only slowly progressive.

For seven recessive NSHI loci, more than one linked family is known: DFNB1 (Guilford et al. 1994*a*; Scott et al. 1995; Brown et al. 1996), DFNB2 (Guilford et al. 1994*b*; Fukushima et al. 1995*a*), DFNB4 (Baldwin et al. 1995; R. J. H. Smith, unpublished data), DFNB7/DFNB11 (Jain et al. 1995; Scott et al. 1996), and DFNB8/DFNB10 (Bonné-Tamir et al. 1996; Veske et al. 1996). It also has been suggested that as many as 50% of recessive NSHI families are linked to DFNB1 (Maw et al. 1995). Of the dominant NSHI loci, only two are known to have several linked families: five families from Europe, Asia, and the United States are linked to DFNA2 (Van Camp et al., in press), and three families from Europe and the United States are linked to DFNA10 (G. Van Camp, R. J. H. Smith, and L. Tranebjaerg, unpublished data).

A number of loci for NSHI have been mapped to overlapping chromosomal regions. In the recessive group, different DFNB numbers have been allocated to the same chromosomal region, on two occasions. First, the candidate regions for DFNB8 and DFNB10 are largely overlapping. Possibly the same gene is responsible for deafness in these two families, although the hearing impairment in the DFNB8 family is postlingual and the DFNB10 family has prelingual hearing impairment. Second, nonoverlapping regions originally were reported for DFNB7 and DFNB11 (Jain et al. 1995; Scott et al. 1996), but improved maps now place both loci within the same interval (R. J. H. Smith, unpublished data).

In the dominant group, three genes—DFNA8, DFNA11, and DFNA12—map to 11q. The candidate regions for the latter two do not overlap, but the candidate region for DFNA8 overlaps with both that for DFNA11 and that for DFNA12. Phenotypically the families fall into two groups: the members from the DFNA8 and DFNA12 families have a prelingual stable hearing

Table 2

Gene Localizations for Autosomal Dominant NSHI

Locus	Location	Frequency	Onset	Type[a]	Reference
DFNA1	5q31	Low	Postlingual	Progressive	Léon et al. (1992)
DFNA2	1p32	High	Postlingual	Progressive	Coucke et al. (1994)
DFNA3	13q12	High	Prelingual	Stable	Chaib et al. (1994)
DFNA4	19q13	Mid/All	Postlingual	Progressive	Chen et al. (1995)
DFNA5	7p15	High	Postlingual	Progressive	Van Camp et al. (1995)
DFNA6	4p16.3	Low	Postlingual	Progressive	Lesperance et al. (1995)
DFNA7	1q21-q23	High	Postlingual	Progressive	Fagerheim et al. (1996)
DFNA8	11q	Mid/All	Prelingual	Stable	Kirschhofer et al. (1996)
DFNA9	14q12-q13	High	Postlingual	Progressive	Manolis et al. (1996)
DFNA10	6q22-q23	Mid/All	Postlingual	Progressive	O'Neill et al. (1996)
DFNA11	11q12.3-q21	Mid/All	Postlingual	Progressive	Tamagawa et al. (1996)
DFNA12	11q22-q24	Mid/All	Prelingual	Stable	G. Van Camp, unpublished data
DFNA13	6p21.3	Mid/All	Postlingual	Progressive	R. J. H. Smith, unpublished data

[a] All loci are responsible for sensorineural hearing loss.

impairment, whereas the DFNA11 family is reported as having postlingual gradually progressive hearing impairment. Perhaps the hypothesis that the same deafness gene is responsible for DFNA8 and DFNA12—and that another deafness gene, which is located in a more centromeric region, is responsible for DFNA11—is the most likely.

In a few cases, both recessive and dominant loci map to the same chromosomal region, suggesting that different mutations in the same gene may lead to recessive or dominant phenotypes: DFNB1 and DFNA3 both map to 13q12, and DFNB2, DFNA8, and DFNA11 colocalize to 11q. Also, DFNB5 and DFNA9 map close to each other, but the candidate regions are nonoverlapping.

Remarkably, linkage to two different regions has been found for DFNB15 (R. J. H. Smith, unpublished). DFNB15 was mapped in a small consanguineous family with autosomal recessive, severe to profound hearing impairment in the affected persons. Linkage to known DFNB genes was excluded, and a genomewide screen using 165 polymorphic markers evenly spaced across the autosomal human genome documented the presence of two regions of homozygosity by descent in affected siblings, one on 3q and the second on 19p. LOD scores over both intervals were identical, at 2.78, which is the maximum obtainable LOD score in this family. It is possible that only one of these two regions of homozygosity contains a genetic defect causing deafness and that the second region of homozygosity has no relation to the deafness. However, digenic inheritance cannot be excluded in this family. Digenic inheritance has been reported before—for example, in a form of retinitis pigmentosa caused by the coinheritance of both a mutation in the peripherin/RDS gene on chromosome 6 and the ROM1 gene on chromosome 11 (Kajiwara et al. 1994).

X-Linked Loci

X-linked NSHI loci have the prefix "DFN" (table 3). DFN1 (Xq22) was first indexed by McKusick in 1966 after the report of a large Norwegian family with progressive NSHI (MIM 3040; Mohr and Mageroy 1960). However, recent reanalysis of this family has revealed additional symptoms, including visual disability, dystonia, fractures, and mental retardation, indicating that this form of hearing impairment is syndromic and therefore should not be included within the NSHI category (Tranebjaerg et al. 1995). The gene for this syndrome, DDP (deafness dystonia peptide), recently has been cloned, but its function remains unknown (Jin et al. 1996). DFN3 (Xq21.1) is characterized by a mixed conductive-sensorineural hearing impairment (Brunner et al. 1988; Wallis et al. 1988; Reardon et al. 1991), the conductive component of which is caused by stapedial fixation. In contrast to other types of conductive hearing impairment, surgical correction is precluded by an abnormal communication between the cerebrospinal fluid and perilymph, which results in leakage (perilymphatic gusher) and complete loss of hearing when the oval window is fenestrated or removed. The DFN3 gene has been identified as the POU3F4 gene (de Kok et al. 1995). Other X-linked NSHI phenotypes include profound prelingual hearing impairment characteristic of both DFN2 (Xq22; Tyson et al. 1996) and DFN4 (Xp21.2; Lalwani et al. 1994), as well as bilateral high-frequency impairment beginning at 5–7 years of age and progressing, by adulthood, to severe to profound hearing impairment, over all frequencies, characteristic of DFN6 (Xp22; del

Table 3

Gene Localizations for X-Linked NSHI

Locus	Location	Frequency	Onset	Type[a]	Reference
DFN1[b]	Xq22	All	Postlingual	Progressive	Tranebjaerg et al. (1995)
DFN2	Xq22	All	Prelingual	Stable	Tyson et al. (1996)
DFN3	Xq21.1	All	Prelingual	Stable (mixed hearing loss)	de Kok et al. (1995)
DFN4	Xp21.2	All	Prelingual	Stable	Lalwani et al. (1994)
DFN5	Reserved[c]				
DFN6	Xp22	High	Postlingual	Progressive	del Castillo et al. (1996)
DFN7	Reserved[c]				
DFN8	Reserved[c]				

[a] Sensorineural hearing loss, except for DFN3, where the hearing loss is mixed sensorineural and conductive.

[b] First described as NSHI but later recognized as syndromic.

[c] Localization reported to HUGO Nomenclature Committee but not yet published.

Castillo et al. 1996). For the DFN5, DFN7, and DFN8 loci, the results are not yet published.

Identified Genes

In spite of the large number of gene loci for NSHI, only two nuclear genes have been cloned. The first, POU3F4, was identified by the study of small deletions in DFN3 patients (de Kok et al. 1995). POU genes constitute a family of transcription factors containing a highly conserved homeodomain and a POU-specific domain. The POU gene family has a function in developmental regulation (Ingraham et al. 1990; Rosenfeld 1991). POU3F4 is expressed in the developing inner ear, brain, kidney, and neural tube (de Kok et al. 1996). Mutations in the POU3F4 gene have been found in nine unrelated DFN3 patients (Bitner-Glindzicz et al. 1995; de Kok et al. 1995, 1996). In six additional DFN3 patients, microdeletions have been found >800 kb proximal to the POU3F4 gene, suggesting the presence of either a second DFN3 gene or sequences involved in the transcription regulation of the POU3F4 gene. Alternatively, these deletions may position the POU3F4 gene in a transcriptionally inactive heterochromatic region (de Kok et al. 1996).

The second nuclear NSHI gene is myosin-VIIa (MYO7A), an unconventional myosin that causes DNFB2 (Ayadi 1996). In general, unconventional myosins (myosin-I, -V, -VI, -VII, -IX, and -X) are important intracellular motor molecules that utilize energy from adenosine triphosphate (ATP) hydrolysis to generate mechanical forces (Hasson et al. 1995). Their N-terminal motor domains share 25%–45% amino acid homology and contain actin- and ATP-binding sites; the C-termini are class-specific tail domains that serve in dimerization, membrane binding, protein binding, and/or enzymatic activities (Cheney et al. 1993; Mooseker and Cheney 1995). Each unconventional myosin class is targeted to a particular subcellular location. In the inner ear, MYO7A is expressed in the inner and outer hair cells (El-Amraoui et al. 1996). Gene expression also occurs in the retina, and mutations in MYO7A have been identified in Usher syndrome type 1b, a recessive form of syndromic hearing impairment characterized by congenital deafness, vestibular dysfunction, and progressive pigmentary retinopathy (Weil et al. 1995).

Mitochondrial Mutations

Hearing impairment often occurs as an additional symptom in syndromic deafness caused by mtDNA defects (reviewed by Reardon and Harding 1995). In many of these cases, ataxia, diabetes, and eye abnormalities are present. However, mitochondrial mutations also can cause clinical pictures with hearing impairment as the sole feature (table 4). In two families, a homoplasmic mutation at nt 1555 in the mitochondrial 12S rRNA gene has been found (Prezant et al. 1993; Matthijs et al. 1996). This mutation also occurs in patients with aminoglycoside-induced ototoxic hearing impairment (Fischel-Ghodsian et al. 1993; Hutchin et al. 1993; Prezant et al. 1993). In two other families, a heteroplasmic mutation at nt 7445 of the $tRNA^{Ser(UCN)}$ gene has been identified (Reid et al. 1994; Fischel-Ghodsian et al. 1995). The penetrance of the hearing impairment caused by these mitochondrial mutations is quite low, suggesting that unidentified genetic or environmental factors play a role in the progression of the hearing impairment.

On-Line Information for NSHI

Easily accessible data summarizing the genetic information on NSHI are available on the Hereditary

Table 4

Mitochondrial Mutations Giving Rise to NSHI

Gene	Mutation	Frequency	Onset	Type[a]	Reference
12S rRNA	A1555G	All	Postlingual	Progressive	Prezant et al. (1993)
$tRNA^{Ser(UCN)}$	T7445C	High	Postlingual	Progressive	Reid et al. (1994)

[a] All loci are responsible for sensorineural hearing loss.

Hearing Loss Homepage (Van Camp and Smith 1996; http://dnalab-www.uia.ac.be/dnalab/hhh). The site is continuously updated and provides information on NSHI loci and genes, including the official name, the chromosomal location, microsatellite markers for linkage analysis, potential mouse homologues, and references. The clinical aspects of the type of hearing impairment also are provided for many loci. Direct links to several databases, including the Genome Database, OMIM, and Medline are included when relevant. The information is maintained in collaboration with many researchers in the field and with Dr. Sue Povey, chairperson of the HUGO Nomenclature Committee.

The Future

Over the past 4 years, there has been an explosion of gene localizations for NSHI, and, as of this moment, 30 chromosomal loci for NSHI have been mapped. Undoubtedly, many more loci will be reported over the next few years. Although only two nuclear genes have been identified, the process of positional cloning is being greatly facilitated by the Human Genome Project and the mapping of expressed sequence tags (ESTs) to specific chromosomal regions. More than 4,000 clones from a cochlear-specific cDNA library (Robertson et al. 1994) have been sequenced and are available on the LENS Web site (http://agave.humgen.upenn.edu/lens) by selecting library 190:Morton Fetal Cochlea. More than 25% of these clones represent new sequences not found in libraries for other tissues, suggesting that they may be expressed only in the cochlea and might be involved specifically in hearing. The specific chromosomal regions to which these ESTs are being mapped are reported on the Whitehead Institute Web site (http://www-genome.wi.mit.edu) and on the Gene Map Web site (http://www.ncbi.nlm.nih.gov/science96/). These initiatives are providing candidate genes for many NSHI loci. It is to be expected that over the next few years several additional genes for NSHI will be cloned and will provide a framework by which to understand the underlying molecular mechanisms involved in auditory function.

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